Observational Study

Medicine®

OPEN

Elective nodal irradiation provides a superior therapeutic modality for lymph node positivity esophageal squamous cell carcinoma patients receiving definitive radiotherapy versus involved-field irradiation

Qiaofang Li, MD, Shuchai Zhu, PhD*, Shuguang Li, MD, Wenzhao Deng, MD

Abstract

This retrospective study was conducted to evaluate the efficacy and safety of elective nodal irradiation (ENI) and involved-field irradiation (IFI) for esophageal squamous cell carcinoma (ESCC) patients treated with intensity-modulated radiotherapy (IMRT).

From January 2006 to December 2012, 644 patients (ENI = 157, IFI = 487) with stage I to IVa ESCC (AJCC 2010) at our institution were analyzed. Propensity score matching (PSM) was used to identify 471 (ENI = 157, IFI = 314) well-balanced patients for comparison. Overall survival (OS) was the primary outcome of the study.

After PSM, the median OS was 26.8 (95% confidence interval [CI], 17.9–35.7) for the ENI arm versus 21.5 (95% CI: 17.9–25.1) months in the IFI arm. The 1-, 3-, 5-year OS were 77.1%, 42.0%, and 26.1% for the ENI arm versus 73.2%, 32.2%, and 19.0% for the IFI arm ($P = .020$). ENI was a significant independent predictor of 5-year OS (1.301 [1.052–1.609]; $P = .015$). Furthermore, patients with stage I/II ESCC or lymph node (LN) positivity in the ENI arm had significantly better 5-year OS than their counterparts in the IFI arm. In addition, for LN positivity patients treated with definitive radiotherapy alone, ENI tended to prolong OS compared with IFI ($P = .035$). The 2 arms were comparable in toxicities.

Using IMRT, ENI is superior to IFI in improving OS of ESCC patients, with acceptable toxicities that were comparable to those to IFI, especially for LN positivity ESCC patients treated with definitive irradiation alone. These results should be confirmed in a large randomized study comparing these 2 modalities.

Abbreviations: CI = confidence interval, CRT = chemoradiotherapy, CT = computed tomography, CTV = clinical target volume, DMFS = distant metastasis-free survival, ENI = elective nodal irradiation, ESCC = esophageal squamous cell carcinoma, GTV = gross tumor volume, IFI = involved-field irradiation, IMRT = intensity-modulated radiotherapy, LN = lymph node, LRFFS = local-regional failure-free survival, LRR = locoregional recurrence, OS = overall survival, PFS = progression-free survival, PSM = propensity score matching, PTV = planning target volume, RT = radiotherapy, SDif = standardized difference.

Keywords: esophageal neoplasms, intensity-modulated, prognosis, propensity score, radiotherapy, survival analysis

1. Introduction

Despite the best available therapeutic regimen, esophageal squamous cell carcinoma (ESCC) patients have a dismal prognosis due to high rates of locoregional recurrence (LRR) and distant metastasis, with a 5-year survival rate of approximate 18%.[1] Radiotherapy (RT) plays an important role for patients with inoperable esophageal cancer. However, ESCC has an extensive and longitudinal interconnecting system of lymphatics in the esophageal wall.[2] As a result, an extended radiation portal design is generally used as the initial irradiation field for esophageal cancer. However, to date, no consensus has been established regarding the extent of the radiation field, especially for elective lymph node (LN) areas, on the outcome by definitive RT or chemoradiation. Clinical practice for determining the clinical target volume (CTV), especially the LN volume, varies. ESCC is prone to spread axially to regional lymphatics and has a high incidence of occult regional LN metastasis. Elective nodal irradiation (ENI) includes the areas at risk for microscopic disease and elective nodal regions, while involved-field irradiation (IFI) includes only the metastatic nodes. Theoretically, it would seem logical to deliver a certain dose to the noninvolved regional LN area at risk for microscopic disease, but the large radiation volume can increase side effects of RT. ENI still encounters criticism from critics suspicious of its survival benefit. A smaller range of CTV, on the other hand, may increase the risk of nodal failure in nonirradiated nodal stations.

To deliver tailored treatment for an optimal outcome, we need to improve the reliability of pretherapeutic staging for RT target delineation. However, currently, there is still lack of direct evidence from high-quality randomized clinical trials. In this retrospective study, we investigated the effect of ENI and IFI on the overall survival (OS) of ESCC patients at our institution and

Editor: Surinder Kumar.

The authors have no funding and conflicts of interest to disclose.

Department of Radiation Oncology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China.

** Correspondence: Shuchai Zhu, Department of Radiation Oncology, The Fourth Hospital of Hebei Medical University, 12 Jiankang Road, Shijiazhuang, Hebei, China (e-mail: sczhu1965@163.com, lqf20006@126.com).*

Medicine (2019) 98:3(e14080)

Received: 5 September 2018 / Received in final form: 17 December 2018 / Accepted: 18 December 2018

http://dx.doi.org/10.1097/MD.0000000000014080

further delineated the prognostic predictors of ESCC outcomes by multivariate analysis.

2. Methods

2.1. Patients

We retrospectively analyzed the clinical data of eligible patients with pathologically proven ESCC who underwent ENI or IFI between January 2006 and December 2012 at our institution. A patient was included in the study if he or she had stage I to Iva ESCC (AJCC 2010); if he or she was suitable for definitive RT with or without chemotherapy; if he or she received intensity-modulated radiotherapy (IMRT) and refused surgery. Patients with incomplete clinicopathologic data were excluded. The study protocol was approved by the local ethics committee at the authors' affiliated institution. Patient consent was not required because of the retrospective nature of the study and patient data were anonymized.

2.2. Treatment

In the IFI arm, the gross tumor volume (GTV) was visualized on computed tomography (CT) and X-ray and/or endoscopic extension. All LNs with a diameter of at least 1 cm in the short axis in CT or that were positive by 18 fluorodeoxyglucose positron emission tomography were defined as GTV-LNs. The CTV was generated by using 0.5 to 0.8 cm radial margin and 2 to 3 cm longitudinal margins to the GTV-primary, and CTV-LNs by using 0.5 cm margin for the GTV-LNs. The planning target volume (PTV) was generated by applying a 5 to 10 mm margin to the CTV, and PTV-LNs by using 0.5 to 0.8 cm margin for CTV-LNs. In the ENI arm, patients received irradiation in the same PTV/PTV-LNs as in the IFI field above. The ENI field (CTV1) was generated as follows: for the supraclavicular area, treatment of higher echelon cervical nodes was considered. For the proximal third of the esophagus, the paraesophageal LNs and the supraclavicular area were treated. For middle lesions, the paraesophageal LNs were treated. For the distal and the gastroesophageal junction, the lesser curvature, celiac axis, and paraesophageal LNs were treated. PTV1 was created by adding margins of 0.5 to 1.0 cm to CTV1 Patients in the IFI arm were treated with 56 to 66 Gy in 95% PTV/PTV-LNs delivered over 5 to 7 weeks at 1.8 to 2 Gy per fraction. In the ENI arm, patients received the same irradiation dose in 95% PTV/PTV-LNs as in the IFI field above, and 50 to 54 Gy (1.8–2.0 Gy per fraction) delivered in 95% PTV1 over 5 to 7 weeks. The radiation dose was $\leq$45 Gy for the spinal cord. The mean lung dose had to be $\leq$20 Gy, and V20 (the lung volume rate receiving over 20 Gy) $\leq$ 30% and V30 $\leq$ 20%. The mean heart dose was $\leq$40 Gy, V30 $\leq$ 40%, and V40 $\leq$ 30%. Six-megavoltage photons were used to deliver radiation by linear accelerators. Chemotherapy was often administered in combination with 5-fluorouracil and taxane, or with platinum-based compounds.

2.3. Follow-up and toxicity criteria

Patients were followed up via physical examination, chest and abdominal CT, gastroenteral endoscopy, and barium esophagography at 3-month intervals for the first 2 years and every 6 months thereafter. The date of the last follow-up was December 31, 2016. Treatment-related toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 5.0).

2.4. Statistical methods

Categorical and continuous variables were compared with the chi-squared test and Student *t* test, respectively. The median follow-up was computed using the reverse Kaplan–Meier method. Patients were considered to be experiencing local failure only if histologic or cytologic evidence was observed in the primary tumor. LN metastases were diagnosed based on the appearance of new nodes in regions where no enlarged nodes had been identified before irradiation. Suspected supraclavicular node recurrences were confirmed by fine-needle aspiration biopsy. OS was the primary endpoint, and calculated from the date of ESCC diagnosis until death or the last follow-up on December 31, 2016. The secondary outcomes were progression-free survival (PFS) and toxicities. PFS was defined as the duration until local-regional recurrence or distant progression, last follow-up or death. Local-regional failure-free survival (LRFFS) was defined as the duration until any recurrence at the initial primary site of disease or in regional LNs, last follow-up or death. Distant metastasis-free survival (DMFS) was defined as the duration until any disease recurrence in a different organ or any failure outside the chest, last follow-up or death. Survival curves were plotted using the Kaplan–Meier method and compared with the log-rank test. Multivariate survival analyses were done using the Cox proportional hazards regression model. To avoid collinearity in the regression models, associations between covariates were assessed using the Wilcoxon rank-sum test. To minimize the potential selection bias, propensity score matching (PSM) analyses were generated using binary logistic regression. Independent variables were entered into the propensity model, including sex, age, tumor location, N stage, tumor length, tumor volume, and RT dose. One-to-two matching between the arms was accomplished using the nearest-neighbor matching method. Standardized difference (SDif) was used to accessed covariate balance. Matched data were analyzed using the Student *t* test or the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables. Propensity scores were estimated using logistic regression. All statistical computations were done using SPSS19.0 (SPSS Inc, Chicago, IL) and R 2.10.1. A 2-sided P value $< .05$ or SDif $\geq$ 10% was statistically significant.

3. Results

3.1. Demographic and baseline variables and treatment characteristics of the study population

The study flowchart is shown in Fig. 1. During the study period, 719 patients with pathologically proven stage I to Iva ESCC underwent ENI or IFI at our institution. Sixty-five were excluded because of incomplete clinicopathologic data and 10 were not included due to discontinued RT. Finally, 644 patients were eligible for inclusion in this retrospective analysis, including 157 patients in the ENI arm and 487 patients in the IFI arm. After PSM, 471 (ENI = 157, IFI = 314) well-balanced pairs of patients were available for outcome comparison (Fig. 2). Their demographic and baseline variables and treatment characteristics are shown in Table 1.

3.2. OS

The patients were followed up for a median duration of 92.9 (95% confidence interval [CI], 88.3–97.6) in the ENI arm and

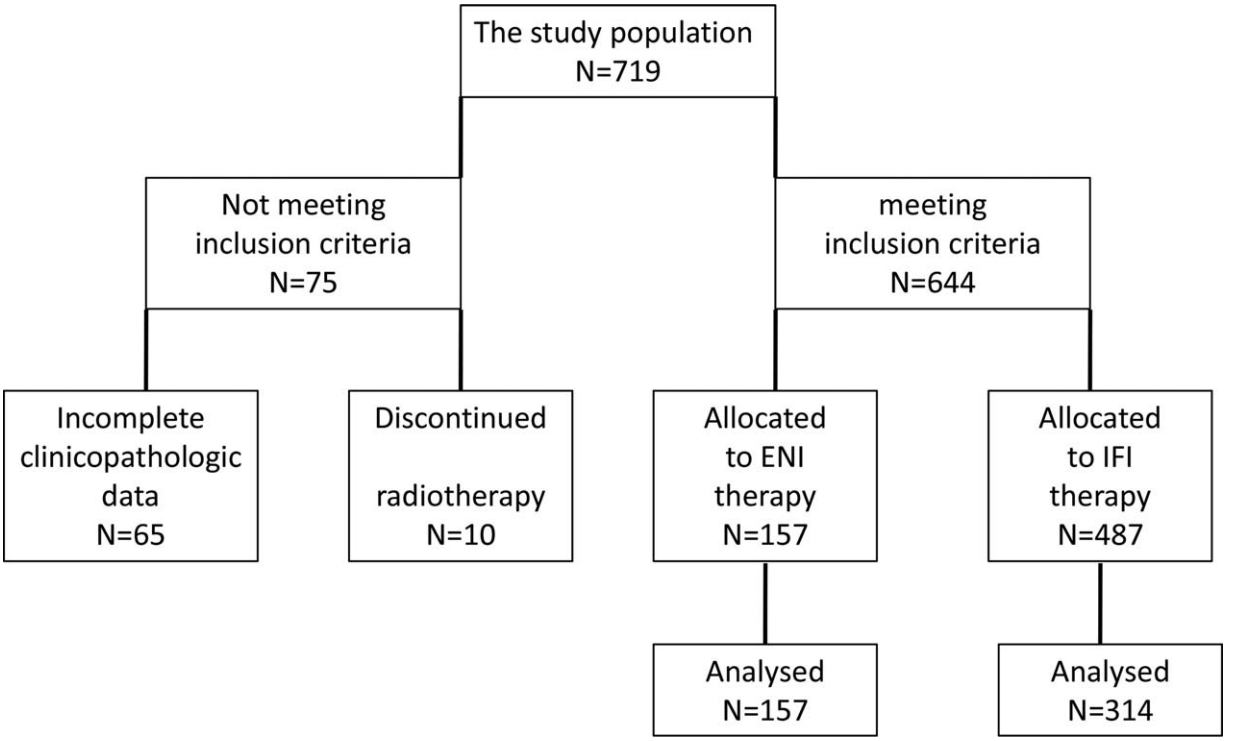

Figure 1. The study flow chart.

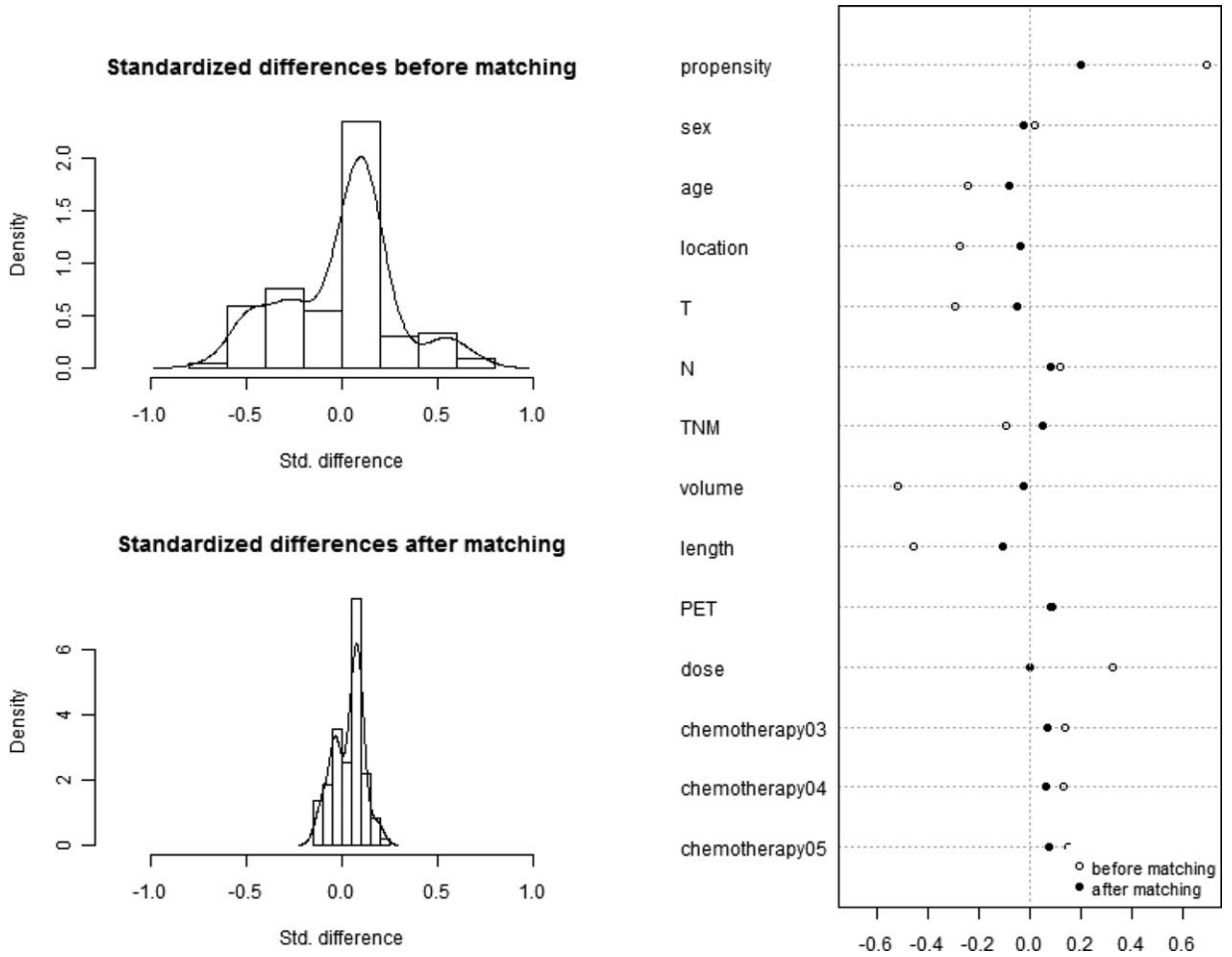

Figure 2. Standardized differences before and after matching.

Table 1

Demographic and baseline variables and treatment characteristics of the study population.

	Entire dataset (N = 644), %				PSM dataset (N = 471), %			
Variables	**ENI (157)**	**IFI (487)**	**SDif, %**	***P***	**ENI (157)**	**IFI (314)**	**SDif, %**	***P***
Sex								
Male	101 (64.3)	318 (65.3)	0.020	.825	101 (64.3)	200 (63.7)	−0.027	.892
Female	56 (35.7)	169 (34.7)			56 (35.7)	114 (36.3)		
Age, y								
≤62	73 (46.5)	167 (34.3)	−0.244	.006	73 (46.5)	133 (42.4)	−0.083	.393
>62	84 (53.5)	320 (65.7)			84 (53.5)	181 (57.6)		
Tumor location								
Upper/middle	138 (87.9)	384 (78.9)	−0.277	.012	138 (87.9)	279 (88.9)	−0.039	.759
Lower	19 (12.1)	103 (21.1)			19 (12.1)	35 (11.1)		
T stage								
T1 + 2	76 (48.4)	164 (33.7)	−0.294	.001	76 (48.4)	141 (44.9)	−0.051	.472
T3 + 4	81 (51.6)	323 (66.3)			81 (51.6)	173 (55.1)		
N stage								
N0	75 (47.8)	261 (53.6)	0.116	.204	75 (47.8)	157 (50.0)	0.083	.648
N+	82 (52.2)	226 (46.4)			82 (52.2)	157 (50.0)		
TNM stage								
I + II	83 (52.9)	234 (48.0)	−0.096	.294	83 (52.9)	174 (55.4)	0.051	.601
III + IVa	74 (47.1)	253 (52.0)			74 (47.1)	140 (44.6)		
Tumor volume, cm^3								
≤50	121 (77.1)	269 (55.2)	−0.518	.000	121 (77.1)	218 (69.4)	−0.023	.082
>50	36 (22.9)	218 (44.8)			36 (22.9)	96 (30.6)		
Tumor length, cm								
≤7	129 (82.2)	315 (64.7)	−0.455	.000	129 (82.2)	242 (77.1)	−0.108	.202
>7	28 (17.8)	172 (35.3)			28 (17.8)	72 (22.9)		
^{18}FDG-PET								
No	100 (63.7)	329 (67.6)	0.080	.372	100 (63.7)	213 (67.8)	0.086	.370
Yes	57 (36.3)	158 (32.4)			57 (36.3)	101 (32.2)		
Radiotherapy dose, Gy	62.2 ± 2.3	61.5 ± 4.4	0.322	.006	62.2 ± 2.3	62.1 ± 3.9	−0.002	.661
Number of chemotherapy cycles								
0	99 (63.1)	334 (68.6)	0.139	.219	99 (63.1)	204 (65.0)	0.069	.812
1–2	23 (14.6)	74 (15.2)			23 (14.6)	48 (15.3)		
≥3	35 (22.3)	79 (16.2)			35 (22.3)	62 (19.7)		
0	99 (63.1)	334 (68.6)	0.129	.317	99 (63.1)	204 (65.0)	0.063	.809
1–3	33 (21.0)	96 (19.7)			33 (21.0)	67 (21.3)		
≥4	25 (15.9)	57 (11.7)			25 (15.9)	43 (13.7)		
0	99 (63.1)	334 (68.6)	0.150	.121	99 (63.1)	204 (65.0)	0.073	.457
1–4	40 (25.5)	121 (24.8)			40 (25.5)	85 (27.1)		
≥5	18 (11.4)	32 (6.6)			18 (11.4)	25 (7.9)		

^{18}FDG-PET = 18 fluorodeoxyglucose positron emission tomography, ENI = elective nodal irradiation, IFI = involved-field irradiation, PSM = propensity score matching, SDif = standardized difference, TNM stage = tumor, node, metastasis stage.

117.6 (95% CI: 110.2–124.9) months in the IFI arm. In total, 644 patients the follow up; 32 patients were lost to follow up due to loss of contact. The median OS was 26.8 (95% CI: 17.9–35.7) for the ENI arm versus 20.0 (95% CI: 18.0–22.0) months for the IFI arm. Moreover, the 1-, 3-, and 5-year OS 77.1%, 42.0%, and 26.1% for the ENI arm versus 70.4%, 29.8%, and 16.3% for the IFI arm ($P = .001$). After PSM, the median OS was 26.8 (95% CI: 17.9–35.7) for the ENI arm versus 21.5 (95% CI: 17.9–25.1) months in the IFI arm. The 1-, 3-, 5-year OS were 77.1%, 42.0%, and 26.1% for the ENI arm versus 73.2%, 32.2%, and 19.0% for the IFI arm ($P = .020$) (Fig. 3A).

Furthermore, our univariate analysis showed that, after PSM, female gender, T1 + 2, N0, stage I/II, tumor length ≤7 cm, tumor volume ≤50 cm^3, chemotherapy, and ENI were associated with significantly better 5-year OS. Multivariable analysis further revealed that female gender, T1 + 2 stage, N0 stage, stage I/II, ≥4 cycles of chemotherapy, and ENI were significant determinants of more favorable 5-year OS (Table 2).

3.3. PFS

The 1-, 3-, and 5-year PFS were 61.8%, 30.6%, and 19.1% for the ENI arm versus 54.8%, 23.4%, and 13.7% for the IFI arm ($P = .010$). After PSM, the 1-, 3-, and 5-year PFS was 61.8%, 30.6%, and 19.1% for the ENI arm versus 56.7%, 25.5%, and 15.9% for the IFI arm ($P = .075$) (Fig. 3B). Furthermore, the ENI arm had a significantly better 5-year LRFFS than the IFI arm (ENI: 22.9% vs IFI: 16.5%) ($P = .012$) (Fig. 3C). However, no difference was observed in DMFS between the ENI and IFI arm (ENI: 19.9% vs IFI: 17.5%) ($P = .098$) (Fig. 3D).

Moreover, univariate analysis showed that, after PSM, female gender, T1 + 2, N0, stage I/II, tumor length ≤7 cm, tumor volume > 50 cm^3, and chemotherapy were associated with significantly better 5-year PFS. Multivariable analysis further demonstrated that female gender, T1 + 2 stage, N0 stage, stage I/II, and ≥4 cycles of chemotherapy were significantly determinants of more favorable 5-year PFS (Table 3). Multivariate survival analyses using the Cox proportional hazards regression model

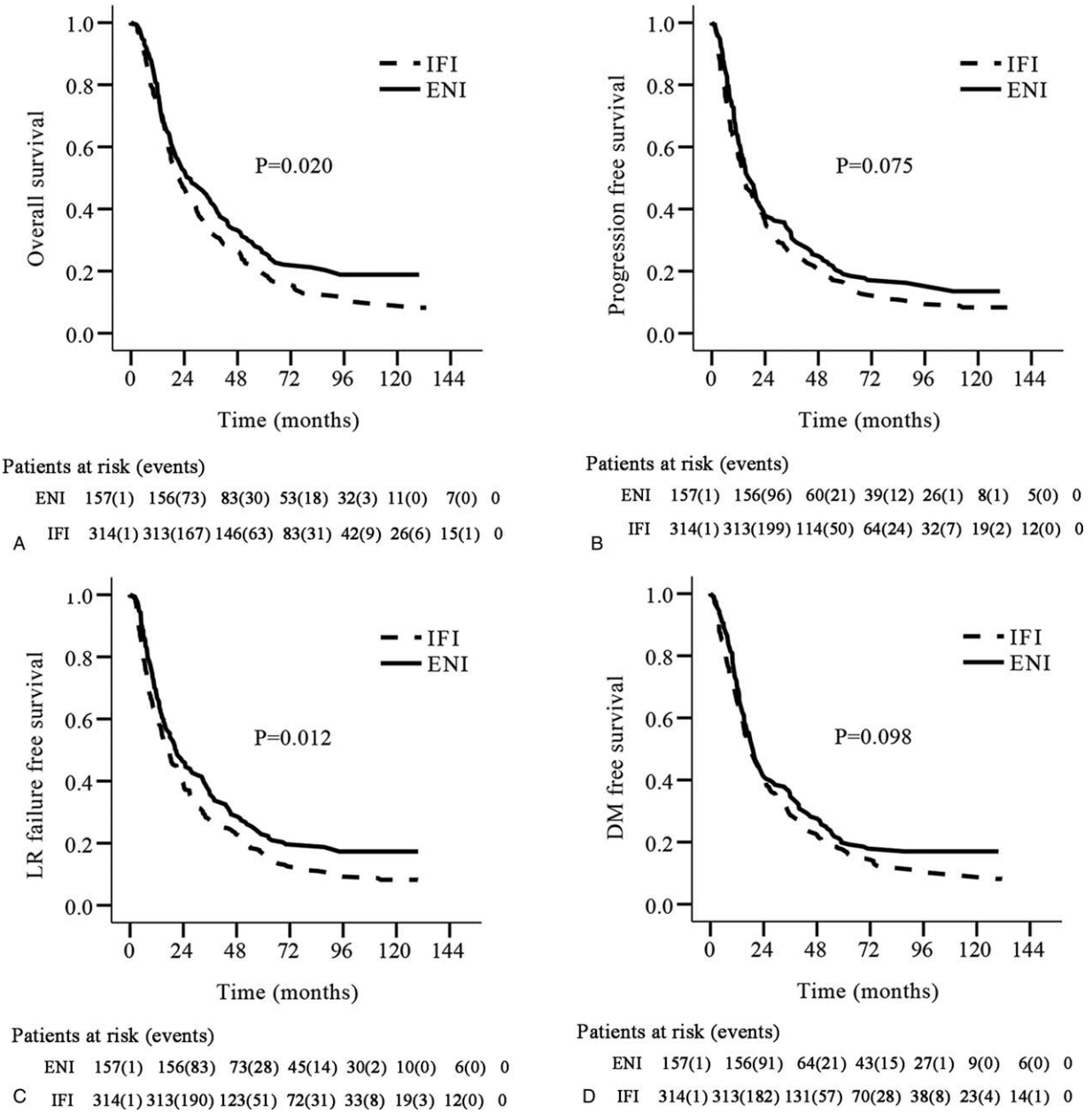

Figure 3. Kaplan–Meier analysis of the IFI and ENI arm after PSM (N = 471). (A) Overall survival, (B) progression-free survival, (C) local-regional failure-free survival, (D) distant metastasis-free survival. ENI = elective nodal irradiation, IFI = involved-field irradiation, PSM = propensity score matching.

showed that female gender, T1 + 2, N0, stage I/II, and ≥4 cycles of chemotherapy were significant predictors of longer LRFFS and DMFS (Table 3). ENI was also a significant prognostic factor for improved LRFFS.

3.4. Toxicities

Grade 3 and 4 acute radiation esophagitis was reported in 3.8% and 0.6% patients in the ENI arm and 4.1% and 0.3% in the IFI arm (Table 4). However, there were no differences in grade ≥ 3 of acute radiation esophagitis (ENI 4.5% vs IFI 4.5%, $P = 1.000$). Grade ≥ 3 acute radiation pneumonitis was seen 2.5% of patients in the ENI arm and 2.9% in the IFI arm ($P = .1000$). Meanwhile, grade ≥ 3 acute hematological adverse events occurred in 7.0% patients in the ENI arm and 5.1% in the IFI arm ($P = .400$). In late toxicities, grade ≥ 3 RT-related toxicities including esophageal stricture, fistula, pulmonary toxicity, and hemorrhage were observed in 14.6% in the ENI arm and 16.6% in the IFI arm ($P = .593$). No other radiation-related toxicity was recorded for the liver and the heart.

3.5. Subgroup analyses after PSM

To identify patients who would benefit from ENI, we carried out a subgroup analysis of OS. We found that patients with stage I/II ESCC or LN positivity in the ENI arm had significantly better 5-year OS than their counterparts in the IFI arm (Table 5). Furthermore, patients with T1 + 2, N0, or stage I/II in the ENI arm had better 5-year PFS than their counterparts in the IFI arm.

Table 2

Multivariate analysis of determinants of OS after PSM.

Variables	OS HR (95% CI)	P
Sex (male or female)	0.755 (0.613–0.930)	.008
T stage (T1 + 2 or T3 + 4)	1.393 (1.091–1.778)	.008
N stage (N0 or N+)	1.382 (1.128–1.692)	.002
TNM stage (I + II or III + Iva)	1.537 (1.199–1.969)	.001
RT field (ENI or IFI)	1.301 (1.052–1.609)	.015
Cycles of chemotherapy (0 or 1–3)	1.080 (0.849–1.374)	.533
Cycles of chemotherapy (0 or ≥4)	0.635 (0.466–0.865)	.004

CI = confidence interval, ENI = elective nodal irradiation, HR = hazards ratio, IFI = involved-field irradiation, OS = overall survival, PSM = propensity score matching, RT = radiotherapy, TNM stage = tumor, node, metastasis stage.

3.6. Subgroup analyses after PSM for the RT group and CRT group, respectively

After PSM, for only 303 patients treated with RT alone, the 1-, 3-, and 5-year OS rates were 78.8%, 40.4%, and 25.3% in the ENI arm, and 73.0%, 32.8%, and 20.0% in the IFI arm ($P = .123$) (Fig. 4A), respectively. In addition, for only 168 patients treated with chemoradiotherapy (CRT) after PSM, the 1-, 3-, and 5-year OS were 82.8%, 48.3%, and 27.6% in the ENI arm, and 75.5%, 31.8%, and 18.2% in the IFI arm ($P = .083$) (Fig. 4B), respectively.

Moreover, we found that patients with LN positivity in the ENI arm had significantly better 5-year OS than their counterparts in the IFI arm in the RT group ($P = .035$), as shown in Table 6. However, there was no significant difference between the ENI and IFI groups in the subgroup analysis for the patients treated with CRT (Table 6).

At the time of analysis, there were no significantly statistical differences in recurrence rates between the ENI and IFI arm in the subgroup analysis of the patients treated with RT or CRT. The data are shown in Table 7.

4. Discussion

In our retrospective study, 471 propensity-score matched ESCC patients received IMRT in the form of ENI or IFI. The results showed that ENI was superior to IFI in prolonging the median OS (ENI: 26.8 [95% CI: 17.9–35.7] months vs IFI: 21.5 [95% CI: 17.9–25.1] months) and 5-year OS (ENI: 26.1% vs IFI: 19.0%; $P = .020$) of ESCC patients. Though a significant difference was observed in 5-year PFS between the 2 arms (ENI: 19.1% vs IFI: 13.7%; $P = .010$); this was not demonstrated in propensity-score matched ESCC patients. Furthermore, we found that the 2 arms were comparable in radiation-associated therapies. These findings demonstrate that ENI offers a safe and more effective therapeutic option versus IFI for ESCC patients.

In a meta-analysis of 757 esophageal cancer patients, Wang et al[3] found no significant difference in OS between patients receiving IFI and ENI. Another meta-analysis[4] found no significant decrease in OS of esophageal cancer patients receiving IFI. Patients in these studies, however, all received chemotherapy. Chemotherapy confers survival benefit on esophageal cancer patients.[5–7] Consistently, our multivariate analysis demonstrated that ≥4 cycles of chemotherapy were a significant predictor of more favorable 5-year OS and 5-year PFS, suggesting the OS benefit of chemotherapy for ESCC patients. Further, our subgroup analysis for patients treated with RT alone or CRT, showed that there were no significant difference in OS between the ENI and IFI arms, indicating that ENI or IFI had similar effect on survival on ESCC patients whether or not receiving chemotherapy, which was similar with the above studies[3,4] and Yun-Jie Cheng's meta-analysis.[8]

However, for N+ patients treated with RT alone, our subgroup analysis showed that a significantly higher 5-year OS in the ENI arm than the IFI arm, which was not similar with the Yun-Jie Cheng's meta-analysis.[8] The reasons may be as follows: the relatively smaller number of cases in literatures selected for meta-analysis, the inconsistent delineation and radiation dosage and radiation techniques for ENI field among different institutions, and the inconsistent nonsurgical staging method in the meta-analysis. However, our study was an original study with a relatively large number of cases, consistent radiation range, and dosage of ENI field in the single institution, all patients received IMRT, and we concluded that ENI's benefit group was the result of ESCC patients with the positive LN in the RT alone group. However, ENI conferred no survival benefit in N0 patients versus IFI for patients receiving chemotherapy or not. For patients with N0 stage, incidental irradiation may play a role in the control of micrometastases in LNs. In IFI, CTV is generated by using 0.5 to 0.8 cm radial margin and 2 to 3 cm longitudinal margin to the GTV-primary in most studies. As such, the peripheral LNs are included in the radiation field. Ji et al[9] showed that IFI may deliver considerable incidental dose to elective regions for patients with T1–4N0M0, which has significant impact on the control of micrometastasis. That ENI did not confer a survival advantage in our N0 patients versus IFI may also be due to a considerable incidental dose to high-risk elective regions in N0 patients receiving IFI.

Stratifying patients based on risk factors could be useful in identifying patients who derive optimal benefit from ENI. We found that compared to IFI, ENI conferred significant benefit in

Table 3

Multivariate analysis of determinants of PFS after PSM.

Variables	PFS HR (95% CI)	P	LRFFS HR (95% CI)	P	DMFS HR (95% CI)	P
Sex (male or female)	0.774 (0.631–0.950)	.014	0.802 (0.653–0.984)	.035	0.765 (0.623–0.940)	.011
T stage (T1 + 2 or T3 + 4)	1.372 (1.082–1.740)	.009	1.348 (1.062–1.713)	.014	1.395 (1.097–1.774)	.007
N stage (N0 or N+)	1.303 (1.068–1.589)	.009	1.324 (1.083–1.617)	.006	1.372 (1.123–1.678)	.002
TNM stage (I + II or III + Iva)	1.337 (1.051–1.701)	.018	1.463 (1.148–1.865)	.002	1.365 (1.070–1.742)	.012
RT field (ENI or IFI)	—	—	1.302 (1.055–1.606)	.014	—	—
Cycles of chemotherapy (0 or 1–3)	1.226 (0.966–1.555)	.094	1.161 (0.914–1.476)	.221	1.155 (0.910–1.466)	.237
Cycles of chemotherapy (0 or ≥4)	0.731 (0.540–0.989)	.042	0.703 (0.518–0.954)	.024	0.690 (0.507–0.939)	.018

CI = confidence interval, DMFS = distant metastasis-free survival, ENI = elective nodal irradiation, HR = hazards ratio, IFI = involved-field irradiation, LRFFS = local-regional failure-free survival, PFS = progression-free survival, PSM = propensity score matching, RT = radiotherapy, TNM = tumor, node, metastasis.

Table 4

Radiation toxicities for propensity-score matched patients (N = 471).

	ENI		IFI	
	N	%	N	%
Radiation esophagitis				
1	75	47.77	95	30.25
2	46	29.30	78	24.84
3	6	3.82	13	4.14
4	1	0.64	1	0.32
5	0	0.00	0	0.00
Radiation pneumonitis				
1	23	14.65	66	21.02
2	14	8.92	35	11.15
3	3	1.91	3	0.96
4	1	0.64	2	0.64
5	0	0.00	4	1.27
Acute hematological adverse events				
1	47	29.94	97	30.89
2	36	22.93	56	17.83
3	10	6.37	16	5.10
4	1	0.64	0	0.00
5	0	0.00	0	0.00

ENI = elective nodal irradiation, IFI = involved-field irradiation.

5-year OS and 5-year PFS on the subgroup of stage I/II ESCC patients, suggesting that earlier stage ESCC patients can be treated effectively with ENI. Few studies have reported outcomes of definitive RT for stage I esophageal cancer patients, and no clear consensus exists regarding radiation fields to be used. There are few reports on the exclusive use of ENI for stage I esophageal cancer. Okawa et al[10] conducted a multi-institutional study of 105 patients with superficial esophageal cancer treated with ENI. LN failure outside the radiation field occurred in 6 patients (6%), whereas LN failure inside the ENI area occurred in only 1 patient (1%). Lee et al[11] assessed the outcomes of extended-field radiation therapy for 23 patients with thoracic superficial esophageal cancer without chemotherapy and found that ENI yielded a 3-year OS of 95.2%. This finding indicates that extended-field RT can be a good option for stage I esophageal cancer patients who are unfit for chemotherapy. In our study, ENI had a trend prolonging OS than IFI for earlier ESCC patients without chemotherapy ($P = .061$), suggesting the OS benefit of ENI for earlier ESCC patients receiving the RT alone. Moreover, our subgroup analysis further indicated that ENI or IFI patients had similar effect on survival on advanced T3 + 4/III + IV stage ESCC patients receiving chemotherapy or not. Regardless of whether radiation is administered using ENI or IFI, regional LN failure is not the main pattern of recurrence in advanced-stage esophageal cancer patients.[12–14]

Table 5

Subgroup analysis of patients in OS with different characteristics after PSM.

Variables	ENI (N = 157)	IFI (N = 314)	5-year OS, %		*P*
			ENI	IFI	
Sex					
Male	101	200	22.8	18.0	.089
Female	56	114	32.1	21.7	.097
T stage					
T1 + 2	76	141	39.5	27.7	.087
T3 + 4	81	173	13.6	12.6	.161
N stage					
N0	75	157	30.7	25.5	.184
N+	82	157	22.0	13.2	.033
TNM stage					
I + II	83	174	38.6	26.9	.019
III + IVa	74	140	12.2	10.0	.217
Cycles of chemotherapy					
0	99	204	25.3	20.0	.123
1–3	33	67	15.2	13.4	.453
≥4	25	43	44.0	25.6	.132

ENI = elective nodal irradiation, IFI = involved-field irradiation, OS = overall survival, PSM = propensity score matching, TNM = tumor, node, metastasis.

Several studies[15–17] failed to demonstrate any significant difference in local/regional failure and regional lymph failure in patients receiving ENI or IFI. We showed that ENI was associated with a significantly better 5-year OS and LRFFS, and suggested that ENI could decrease LRR in the elective field, thus impacting on OS. Occult recurrence and micrometastases to regional LNs may escape detection by currently available diagnostic methods, even at the time of presentation.[18] ENI may exert a prophylactic effect by suppressing micrometastases to regional LNs, influencing the survival of patients with positive LN treated with RT alone. We speculate that prophylactic radiation by ENI without chemotherapy for ESCC patients with occult recurrence and micrometastases to regional LNs may improve therapeutic outcome, especially for positive LN ESCC patients received RT alone.

RT for esophageal cancer is associated with toxicities. The concurrent use of chemotherapy during RT can result in increased toxicities. Ishikura et al[19] investigated long-term toxicities of definitive CRT using ENI for esophageal cancer and found that 10.3% patients experienced grade 3 or greater pericarditis and 9.0% patients died of cardiopulmonary diseases. In the RTOG 85-01 study,[20] 10% patients treated with CRT experienced life-threatening toxicities, while 2% of patients receiving RT alone experienced acute grade 4 toxicities without fatalities due to toxic effect. This finding suggests that patients receiving concurrent ENI and chemotherapy may experience more severe radiation-induced toxicities. However, the patients in these studies were not treated with intensity-modulated radiation therapy, which is implemented for sparing normal organs and tight PTV planning and provides ENI with conformal planning.[2,21] Lee et al[11] showed that there was no grade 3 adverse event, and acute and chronic radiation pneumonitis and esophagitis were acceptable for stage I esophageal cancer patients using ENI. Liu et al[16] also indicated that with better protection of normal organs and proper patient selection, no difference was found in the incidence of grade ≥3 treatment-emergent esophageal and lung toxicities of ENI and IFI with the application of intensity-modulated radiation therapy. Our study showed that the extended field radiation therapy with or without chemotherapy for inoperable esophageal cancer patients produced reasonable treatment outcomes without significant toxicities of grade 3 or higher using intensity-modulated radiation therapy. Therefore, the adverse events of extended-field irradiation can be reduced by the use of intensity-modulated radiation therapy. We may improve outcomes of ENI using intensity-modulated radiation therapy without increasing toxicities.

However, our study has inherent limitations. First, patients with stage I/II ESCC in our study were mostly not suitable for surgery or refused to receive surgery. Second, as a retrospective analysis, treatment differed for patients in terms of radiation dose and in techniques used over the span of the study. Third, more

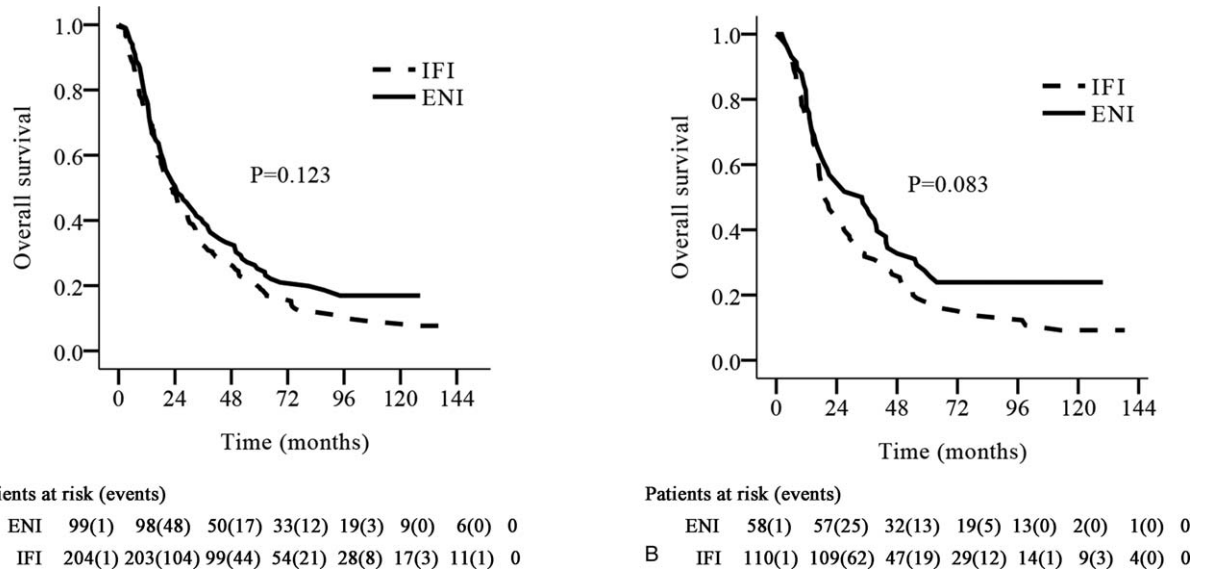

Figure 4. Kaplan–Meier analysis of the IFI and ENI arm for patients treated with RT alone and CRT after PSM. (A) Overall survival for the RT alone group, (B) overall survival for the CRT group. CRT = chemoradiotherapy, ENI = elective nodal irradiation, IFI = involved-field irradiation, PSM = propensity score matching, RT = radiotherapy.

Table 6

Subgroup analysis of OS after PSM in the RT group and CRT group, respectively.

	RT group (5-year OS), %			CRT group (5-year OS), %		
Variables	**ENI**	**IFI**	***P***	**ENI**	**IFI**	***P***
Sex						
Male	22.4	16.8	.155	23.3	19.8	.408
Female	29.3	24.4	.453	40.0	13.8	.065
T stage						
T1 + 2	37.3	26.1	.143	44.0	30.6	.359
T3 + 4	12.5	15.0	.754	15.2	8.2	.077
N stage						
N0	26.5	25.5	.791	38.5	25.5	.107
N+	24.0	13.7	.035	18.8	12.7	.429
TNM stage						
I + II	36.2	25.2	.061	44.0	30.4	.152
III + IVa	9.8	12.8	.877	15.2	5.6	.099

CRT = chemoradiotherapy, ENI = elective nodal irradiation, IFI = involved-field irradiation, OS = overall survival, PSM = propensity score matching, RT = radiotherapy, TNM = tumor, node, metastasis.

Table 7

Subgroup analysis of patterns of treatment failure after PSM in the RT group and CRT group, respectively.

	RT group			CRT group		
	No. of patients, N (%)			No. of patients, N (%)		
Variables	**ENI (N = 99)**	**IFI (N = 204)**	***P***	**ENI (N = 58)**	**IFI (N = 110)**	***P***
Total recurrence	59 (59.6)	117 (57.4)	.711	40 (69.0)	77 (70.0)	.890
Primary tumor recurrence	33 (33.3)	74 (36.3)	.615	20 (34.5)	37 (33.6)	.912
Cervical lymph nodes recurrence	5 (5.1)	6 (2.9)	.347	6 (10.3)	10 (9.1)	.792
Mediastinal lymph nodes recurrence	6 (6.1)	8 (3.9)	.397	5 (8.6)	9 (8.2)	1.000
Abdominal lymph nodes recurrence	1 (1.0)	9 (4.4)	.175	8 (13.8)	10 (9.1)	.349
Primary tumor and regional recurrence	39 (39.4)	88 (43.1)	.536	33 (56.9)	57 (51.8)	.530
Primary tumor and distant recurrence	28 (28.3)	51 (25.0)	.542	17 (29.3)	40 (36.4)	.359
Both locoregional and distant recurrence	8 (8.1)	22 (10.8)	.460	107 (17.2)	20 (18.2)	.880

CRT = chemoradiotherapy, ENI = elective nodal irradiation, IFI = involved-field irradiation, No. = number, PSM = propensity score matching, RT = radiotherapy.

advanced techniques for clinical staging of disease have come into service over the span of the study and functional imaging techniques were not available for all patients, which may have led to diagnostic underestimation. Fourth, although PSM was performed to minimize the confounding effect, the effects of unmeasured confounders, which are intrinsic bias of retrospective studies, were inevitable.

5. Conclusion

In conclusion, using intensity-modulated radiation therapy, ENI is superior to IFI in improving OS of ESCC patients, with acceptable toxicities that were comparable to those to IFI, especially for LN positivity ESCC patients treated with definitive irradiation alone. These results should be confirmed in a large randomized study comparing these 2 modalities.

Author contributions

Conceptualization: Shuchai Zhu, Shuguang Li.
Data curation: Qiaofang Li, Shuchai Zhu, Shuguang Li.
Formal analysis: Qiaofang Li, Shuchai Zhu.
Investigation: Qiaofang Li, Shuchai Zhu.
Methodology: Qiaofang Li, Shuchai Zhu.
Project administration: Shuchai Zhu.
Resources: Qiaofang Li, Shuchai Zhu.
Software: Qiaofang Li, Wenzhao Deng.
Supervision: Qiaofang Li, Shuchai Zhu.
Validation: Shuchai Zhu.
Visualization: Shuchai Zhu.
Writing – original draft: Qiaofang Li.
Writing – review & editing: Shuchai Zhu.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2017;67:7–30.
[2] Van De Voorde L, Larue RT, Pijls M, et al. A qualitative synthesis of the evidence behind elective lymph node irradiation in oesophageal cancer. Radiother Oncol 2014;113:166–74.
[3] Wang X, Miao C, Chen Z, et al. Can involved-field irradiation replace elective nodal irradiation in chemoradiotherapy for esophageal cancer? A systematic review and meta-analysis. Onco Targets Ther 2017; 10:2087–95.
[4] Du D, Song T, Liang X, et al. Concurrent chemoradiotherapy with elective lymph node irradiation for esophageal cancer: a systemic review and pooled analysis of the literature. Dis Esophagus 2017;30:1–9.
[5] Prenzel KL, König A, Schneider PM, et al. Reduced incidence of nodal micrometastasis after major response to neoadjuvant chemoradiation in locally advanced esophageal cancer. Ann Surg Oncol 2007;14:954–9.
[6] Matsuyama J, Doki Y, Yasuda T, et al. The effect of neoadjuvant chemotherapy on lymph node micrometastases in squamous cell carcinomas of the thoracic esophagus. Surgery 2007;141:570–80.
[7] Chen J, Pan J, Liu J, et al. Postoperative radiation therapy with or without concurrent chemotherapy for node-positive thoracic esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2013;86:671–7.
[8] Cheng YJ, Jing SW, Zhu LL, et al. Comparison of elective nodal irradiation and involved-field irradiation in esophageal squamous cell carcinoma: a meta-analysis. J Radiat Res 2018;59:604–15.
[9] Ji K, Zhao L, Yang C, et al. Three-dimensional conformal radiation for esophageal squamous cell carcinoma with involved-field irradiation may deliver considerable doses of incidental nodal irradiation. Radiat Oncol 2012;7:200.
[10] Okawa T, Tanaka M, Kita-Okawa M, et al. Superficial esophageal cancer: multicenter analysis of results of definitive radiation therapy in Japan. Radiology 1995;196:271–4.
[11] Lee DY, Moon SH, Cho KH, et al. Treatment outcomes of extended-field radiation therapy for thoracic superficial esophageal cancer. Radiat Oncol 2017;35:241–8.
[12] Morota M, Gomi K, Kozuka T, et al. Late toxicity after definitive concurrent chemoradiotherapy for thoracic esophageal carcinoma. Int J Radiat Oncol Biol Phys 2009;75:122–8.
[13] Button MR, Morgan CA, Croydon ES, et al. Study to determine adequate margins in radiotherapy planning for esophageal carcinoma by detailing patterns of recurrence after definitive chemoradiotherapy. Int J Radiat Oncol Biol Phys 2009;73:818–23.
[14] Zhao K, Ma JB, Liu G, et al. Three-dimensional conformal radiation therapy for esophageal squamous cell carcinoma: is elective nodal irradiation necessary? Int J Radiat Oncol Biol Phys 2010;76:446–51.
[15] Ma JB, Song YP, Yu JM, et al. Feasibility of involved-field conformal radiotherapy for cervical and upper-thoracic esophageal cancer. Onkologie 2011;34:599–604.
[16] Liu M, Zhao K, Chen Y, et al. Evaluation of the value of ENI in radiotherapy for cervical and upper thoracic esophageal cancer: a retrospective analysis. Radiat Oncol 2014;9:232.
[17] Yamashita H, Okuma K, Wakui R, et al. Details of recurrence sites after elective nodal irradiation (ENI) using 3D-conformal radiotherapy (3D-CRT) combined with chemotherapy for thoracic esophageal squamous cell carcinoma—a retrospective analysis. Radiother Oncol 2011;98: 255–60.
[18] Izbicki JR, Hosch SB, Pichlmeier U, et al. Prognostic value of immunohistochemically identifiable tumor cells in lymph nodes of patients with completely resected esophageal cancer. N Engl J Med 1997;337:1188–94.
[19] Ishikura S, Nihei K, Ohtsu A, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003;21:2697–702.
[20] Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Arm. JAMA 1999;281:1623–7.
[21] Jiang L, Zhao X, Meng X, et al. Involved field irradiation for the treatment of esophageal cancer: is it better than elective nodal irradiation? Cancer Lett 2015;357:69–74.